

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

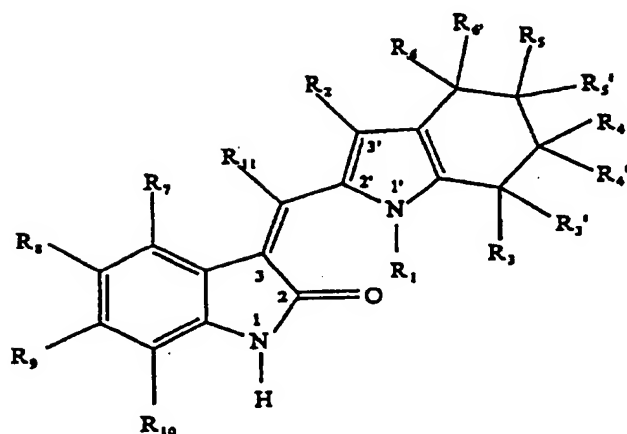
1. – 6. (canceled)

7. (original) An optionally substituted 3-[(tetrahydroindole-2-yl)methylene]-2-indolinone or 3-[(cyclopentano-b-pyrrol-2-yl)methylene]-2-indolinone compound.

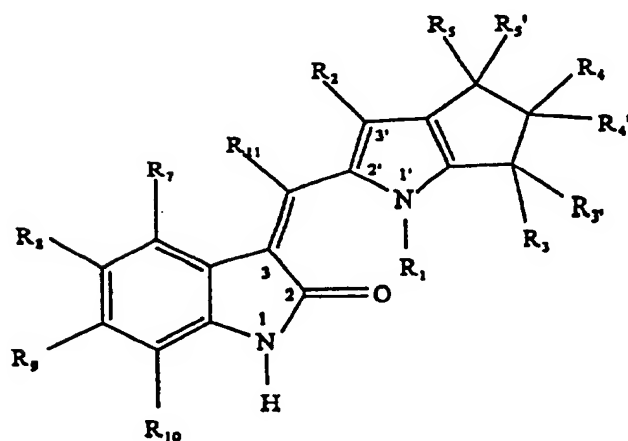
8. (amended) The indolinone compound of claim 7 of formula XIX or

XX,

XIX



XX



or a pharmaceutically acceptable salt, isomer, metabolite, ester, amide, or prodrug thereof  
where (a) R<sub>1</sub> is selected from the group consisting of,

- (i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) ketone of formula  $-\text{CO}-\text{R}_{12}$ , where  $\text{R}_{12}$  is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula  $-(\text{R}_{13})_n-\text{COOH}$  or ester of formula  $-(\text{R}_{14})_m-\text{COO}-\text{R}_{15}$ , where  $\text{R}_{13}$ ,  $\text{R}_{14}$ , and  $\text{R}_{15}$  are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and  $n$  and  $m$  are independently 0 or 1;
- (v) a sulfone of formula  $-(\text{SO}_2)-\text{R}_{16}$ , where  $\text{R}_{16}$  is selected from the group consisting of alkyl or a five or six membered heterocyclic ring, where the ring is optionally substituted with an alkyl moiety;
- (vi)  $-(\text{R}_{17})_n-(\text{indole-1-yl})$  or  $-(\text{R}_{18})_m-\text{CHOH}-(\text{R}_{19})_p-(\text{indole-1-yl})$ , where the indole moiety is optionally substituted with an aldehyde and  $\text{R}_{17}$ ,  $\text{R}_{18}$ , and  $\text{R}_{19}$  are alkyl and  $n$ ,  $m$ , and  $p$  are independently 0 or 1;
- (vii) taken together with a 2' substituent of the indole ring forms a tricyclic moiety, where each ring in the tricyclic moiety is a five or six membered heterocyclic ring;
- (b)  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_3'$ ,  $\text{R}_4$ ,  $\text{R}_4'$ ,  $\text{R}_5$ ,  $\text{R}_5'$ ,  $\text{R}_6$  and  $\text{R}_6'$  are selected from the group consisting of,
  - (i) hydrogen;
  - (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

- (iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iv) ketone of formula  $-\text{CO}-\text{R}_{20}$ , where  $\text{R}_{20}$  is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (v) a carboxylic acid of formula  $-(\text{R}_{21})_n-\text{COOH}$  or ester of formula  $-(\text{R}_{22})_m-\text{COO}-\text{R}_{23}$ , where  $\text{R}_{21}$ ,  $\text{R}_{22}$ , and  $\text{R}_{23}$  are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (vi) halogen;
- (vii) an alcohol of formula  $-(\text{R}_{24})_m-\text{OH}$  or an ether of formula  $-(\text{R}_{24})_n-\text{O}-\text{R}_{25}$ , where  $\text{R}_{24}$  and  $\text{R}_{25}$  are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (viii)  $-\text{NR}_{26}\text{R}_{27}$ , where  $\text{R}_{26}$  and  $\text{R}_{27}$  are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (ix)  $-\text{NHCOR}_{28}$ , where  $\text{R}_{28}$  is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (x)  $-\text{SO}_2\text{NR}_{29}\text{R}_{30}$ , where  $\text{R}_{29}$  and  $\text{R}_{30}$  are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (xi) any two of  $\text{R}_3$ ,  $\text{R}_3'$ ,  $\text{R}_4$ ,  $\text{R}_4'$ ,  $\text{R}_5$ ,  $\text{R}_5'$ ,  $\text{R}_6$ , or  $\text{R}_6'$  taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;
- (c)  $\text{R}_7$ ,  $\text{R}_8$ ,  $\text{R}_9$ , and  $\text{R}_{10}$  are independently selected from the group consisting of,
  - (i) hydrogen;

- (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iv) ketone of formula  $-\text{CO}-\text{R}_{31}$ , where  $\text{R}_{31}$  is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (v) a carboxylic acid of formula  $-(\text{R}_{32})_n-\text{COOH}$  or ester of formula  $-(\text{R}_{33})_m-\text{COO}-\text{R}_{34}$ , where  $\text{R}_{32}$ ,  $\text{R}_{33}$ , and  $\text{R}_{34}$  are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and  $n$  and  $m$  are independently 0 or 1;
- (vi) halogen;
- (vii) an alcohol of formula  $-(\text{R}_{35})_m-\text{OH}$  or an ether of formula  $-(\text{R}_{35})_n-\text{O}-\text{R}_{36}$ , where  $\text{R}_{35}$  and  $\text{R}_{36}$  are independently chosen from the group consisting of alkyl or a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (viii)  $-\text{NR}_{37}\text{R}_{38}$ , where  $\text{R}_{37}$  and  $\text{R}_{38}$  are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (ix)  $-\text{NHCOR}_{39}$ , where  $\text{R}_{39}$  is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (x)  $-\text{SO}_2\text{NR}_{40}\text{R}_{41}$ , where  $\text{R}_{40}$  and  $\text{R}_{41}$  are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

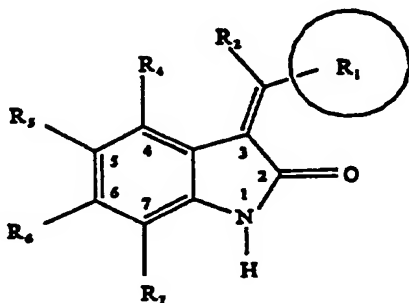
- (xi) any two of  $R_7$ ,  $R_8$ ,  $R_9$ , or  $R_{10}$  taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring; and
- (d)  $R_{11}$  is hydrogen or alkyl.

9. (amended) An indolinone compound having a substituent at the 5 position of the oxindole ring, where the substituent at the 5 position of the oxindole ring is selected from the group consisting of

- (a) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (b) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (c) a ketone of formula  $-\text{CO}-R_{10}$ , where  $R_{10}$  is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (d) a carboxylic acid of formula  $-(R_{11})_n-\text{COOH}$  or ester of formula  $-(R_{12})_m-\text{COO}-R_{13}$ , where  $R_{11}$ ,  $R_{12}$ , and  $R_{13}$  are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (e) halogen;
- (f) an alcohol of formula  $-(R_{14})_m-\text{OH}$  or an ether of formula  $-(R_{14})_n-\text{O}-R_{15}$ , where  $R_{14}$  and  $R_{15}$  are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (g)  $-\text{NR}_{16}R_{17}$ , where  $R_{16}$  and  $R_{17}$  are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

- (h)  $\text{-NHCOR}_{18}$ , where  $\text{R}_{18}$  is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (i)  $\text{-SO}_2\text{NR}_{19}\text{R}_{20}$ , where  $\text{R}_{19}$  and  $\text{R}_{20}$  are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (j) any two of  $\text{R}_4$ ,  $\text{R}_5$ ,  $\text{R}_6$ , or  $\text{R}_7$  taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring.

10. (amended) The compound of claim 9 of the following formula,



where (a)  $\text{R}_5$  is selected from the group consisting of,

- (i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

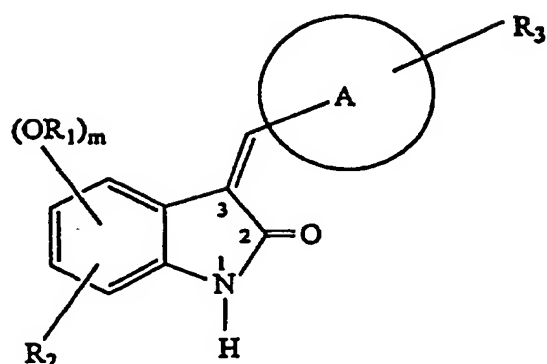
- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) a ketone of formula  $-\text{CO}-\text{R}_{10}$ , where  $\text{R}_{10}$  is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula  $-(\text{R}_{11})_n-\text{COOH}$  or ester of formula  $-(\text{R}_{12})_m-\text{COO}-\text{R}_{13}$ , where  $\text{R}_{11}$ ,  $\text{R}_{12}$ , and  $\text{R}_{13}$  are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (v) halogen;
- (vi) an alcohol of formula  $-(\text{R}_{14})_m-\text{OH}$  or an ether of formula  $-(\text{R}_{14})_n-\text{O}-\text{R}_{15}$ , where  $\text{R}_{14}$  and  $\text{R}_{15}$  are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (vii)  $-\text{NR}_{16}\text{R}_{17}$ , where  $\text{R}_{16}$  and  $\text{R}_{17}$  are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (viii)  $-\text{NHCOR}_{18}$ , where  $\text{R}_{18}$  is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (ix)  $-\text{SO}_2\text{NR}_{19}\text{R}_{20}$ , where  $\text{R}_{19}$  and  $\text{R}_{20}$  are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (x) any two of  $\text{R}_4$ ,  $\text{R}_5$ ,  $\text{R}_6$ , or  $\text{R}_7$  taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;
- (b)  $\text{R}_1$  is selected from the group consisting of a five, six, eight, nine, and ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more substituents selected from the group consisting of



- (i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) a ketone of formula  $-\text{CO}-\text{R}_{21}$ , where  $\text{R}_{21}$  is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula  $-(\text{R}_{22})_n-\text{COOH}$  or ester of formula  $-(\text{R}_{23})_m-\text{COO}-\text{R}_{24}$ , where  $\text{R}_{22}$ ,  $\text{R}_{23}$ , and  $\text{R}_{24}$  are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (v) halogen;
- (vi) an alcohol of formula  $-(\text{R}_{25})_m-\text{OH}$  or an ether of formula  $-(\text{R}_{25})_n-\text{O}-\text{R}_{26}$ , where  $\text{R}_{25}$  and  $\text{R}_{26}$  are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (vii)  $-\text{NR}_{27}\text{R}_{28}$ , where  $\text{R}_{27}$  and  $\text{R}_{28}$  are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (viii)  $-\text{NHCOR}_{29}$ , where  $\text{R}_{29}$  is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (ix)  $-\text{SO}_2\text{NR}_{30}\text{R}_{31}$ , where  $\text{R}_{30}$  and  $\text{R}_{31}$  are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (c)  $\text{R}_4$ ,  $\text{R}_6$ , and  $\text{R}_7$  are independently selected from the group consisting of,

- (i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) a ketone of formula  $-\text{CO}-\text{R}_{32}$ , where  $\text{R}_{32}$  is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula  $-(\text{R}_{33})_n-\text{COOH}$  or ester of formula  $-(\text{R}_{34})_m-\text{COO}-\text{R}_{35}$ , where  $\text{R}_{33}$ ,  $\text{R}_{34}$  and  $\text{R}_{35}$  are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (v) halogen;
- (vi) an alcohol of formula  $-(\text{R}_{36})_m-\text{OH}$  or an ether of formula  $-(\text{R}_{36})_n-\text{O}-\text{R}_{37}$ , where  $\text{R}_{36}$  and  $\text{R}_{37}$  are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and  $m$  and  $n$  are independently 0 or 1;
- (vii)  $-\text{NR}_{38}\text{R}_{39}$ , where  $\text{R}_{38}$  and  $\text{R}_{39}$  are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (viii)  $-\text{NHCOR}_{40}$ , where  $\text{R}_{40}$  is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (ix)  $-\text{SO}_2\text{NR}_{41}\text{R}_{42}$ , where  $\text{R}_{41}$  and  $\text{R}_{42}$  are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring; and
- (d)  $\text{R}_2$  is hydrogen or alkyl.

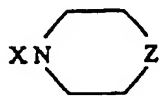
11. (original) A compound having formula XXI, wherein:



XXI

- (a)  $A$  is a five or six membered ring comprised of atoms selected from the group consisting of oxygen, carbon, sulfur and nitrogen;
- (b)  $m$  is zero, 1, or 2;
- (c)  $R_1$  is hydrogen,  $C_1$ - $C_6$  alkyl or  $C_2$ - $C_6$  alkanoyl;
- (d) one of  $R_2$  and  $R_3$  independently is hydrogen and the other is a substituent selected from:
  - (1) a  $C_1$ - $C_6$  alkyl group substituted by 1, 2 or 3 hydroxy groups;
  - (2)  $SO_3R_4$  in which  $R_4$  is hydrogen or  $C_1$ - $C_6$  alkyl unsubstituted or substituted by 1, 2 or 3 hydroxy groups;

- (3)  $\text{SO}_2\text{NHR}_5$  in which  $\text{R}_5$  is as  $\text{R}_4$  defined above or  $\alpha\text{-(CH}_2)_n\text{-N(C}_1\text{-C}_6\text{ alkyl)}_2$  group in which  $n$  is 2 or 3;
- (4)  $\text{COOR}_6$  in which  $\text{R}_6$  is  $\text{C}_1\text{-C}_6$  alkyl unsubstituted or substituted by phenyl or by 1, 2 or 3 hydroxy groups or phenyl;
- (5)  $\text{CONHR}_7$ , in which  $\text{R}_7$  is hydrogen, phenyl or  $\text{C}_1\text{-C}_6$  alkyl substituted by 1, 2 or 3 hydroxy groups or by phenyl;
- (6)  $\text{NHSO}_2\text{R}_8$  in which  $\text{R}_8$  is  $\text{C}_1\text{-C}_6$  alkyl or phenyl unsubstituted or substituted by halogen or by  $\text{C}_1\text{-C}_4$  alkyl;
- (7)  $\text{N(R}_9)_2$ ,  $\text{NHR}_9$  or  $\text{OR}_9$  wherein  $\text{R}_9$  is  $\text{C}_2\text{-C}_6$  alkyl substituted by 1, 2 or 3 hydroxy groups;
- (8)  $\text{NHCOR}_{10}$ ,  $\text{OOCR}_{10}$  or  $\text{CH}_2\text{OOCR}_{10}$  in which  $\text{R}_{10}$  is  $\text{C}_1\text{-C}_6$  alkyl substituted by 1, 2 or 3 hydroxy groups;
- (9)  $\text{NHCONH}_2$ ;  $\text{NH-C(NH}_2\text{)=NH}$ ;  $\text{C(NH}_2\text{)=NH}$ ;  $\text{CH}_2\text{NHC(NH}_2\text{)=NH}$ ;  $\text{CH}_2\text{NH}_2$ ;  $\text{OPO(OH)}_2$ ;  $\text{CH}_2\text{OPO(OH)}_2$ ;  $\text{PO(OH)}_2$ ; or a



wherein  $X$  is selected from the group consisting of  $\text{CH}_2$ ,  $\text{SO}_2$ ,  $\text{CO}$ , or  $\text{NHCO(CH}_2)_p$  in which  $p$  is 1, 2, or 3 and  $Z$  is  $\text{CH}_2$ ,  $\text{O}$  or  $\text{N-R}_{11}$  in which  $\text{R}_{11}$  is hydrogen or is as  $\text{R}_9$  defined above.

12. (original) A method of making an indolinone compound of any one of claims 5-11 comprising the steps of reaching an appropriate aldehyde and oxindole and separating the indolinone from the aldehyde and oxindole reactants.

13. (original) A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier or excipient and (ii) a compound according to any one of claims 5-11.

14. (original) A method for treating a disease related to unregulated tyrosine kinase signal transduction, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to anyone of claims 5-11.

15. (original) A method for regulating tyrosine kinase signal transduction comprising administering to a subject a therapeutically effective amount of a compound according to any one of claims 5-11.

16. (original) A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

- (a) administering a compound of any one-of claims 5-11 to an organism; and
- (b) promoting or disrupting the abnormal interaction.

17. (original) A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

- (a) administering a compound of any one of claims 5-11 to an organism; and
- (b) promoting or disrupting the abnormal interaction.